REMARKS

At the outset, Applicant would like to thank Examiners Amanda Shaw and Dave Nguyen for the courtesy of a telephonic interview with the undersigned on November 2, 2009. Participants in the telephonic interview included: Examiner Shaw, Examiner Nguyen, John Murphy, Ph.D. and the undersigned, Sarah J. Fashena, Ph.D. During the telephonic interview, Applicant's representatives described the claimed method and clarified aspects of the method believed to render the instant claims patentable over the prior art. Amendments to the claims to underscore these aspects of the methods were also discussed. The Examiners' comments responsive thereto are gratefully acknowledged.

Claims 4 and 27-36 are currently pending. Claims 4, 35, and 36 are amended herein to clarify the claimed subject matter. Accordingly, instant claims 4 and 27-36 are under consideration.

Any amendment, however, is not to be construed as abandonment of any subject matter of the originally filed application. Accordingly, it is to be understood that Applicant reserves the right to reintroduce subject matter deleted from the application by the foregoing amendments and to file one or more divisional, continuation, and/or continuation in part applications directed to such subject matter.

Support for amendment to the claims is found throughout the specification and in the original claims. More particularly, support for amendment to claims 4, 35, and 36 is found, for example, in original claim 4 and at page 14, lines 9-11; at page 16, line 25 through to page 17, line 2; at page 13, lines 30-31; and in Figure 2. No issue of new matter is introduced by these amendments.

Rejections under 35 USC § 103

Claims 4, 27-28, 30-31, 33, and 34-36 are rejected under § 103(a) as allegedly unpatentable over Balasubramanisn [*sic*], which should read Balasubramanian et al. (WO 01/57248; published 9/2001) as evidenced by Cheeseman [United States Patent Number (USPN) 5,302,509; issued 1994] in view of Soper et al. (USPN 5,846,727) and Parker et al. (USPN

5,565,323). In view of the clarifying amendments to the claims and arguments presented herein, this rejection is respectfully traversed.

Responsive thereto, Applicant asserts that the combined references do not teach or suggest all elements of the claimed invention. The claims require, *inter alia*, "removing the complementary copy of each of the template sequences from the array, thereby regenerating the immobilised single-stranded template molecules on the array" as recited in step (c) of claims 4 and 35 or "removing the complementary copy of each of the template sequences to recover an array of sequenced immobilised single-stranded template nucleic acid molecules" as recited in step (c) of claim 36. As detailed herein below, none of the references when considered alone or in combination teaches a method that calls for a step directed to regenerating an array of immobilised single-stranded template molecules or recovering an array of sequenced immobilised single-stranded template nucleic acid molecules. Applicant, therefore, asserts that the combined disclosures of Balasubramanian et al., Cheeseman, Soper et al., and Parker et al. fail to teach or suggest all of the elements of the instant claims and thus, fail to adversely impact the patentability of the claimed method.

The Office Action acknowledges that Balasubramanian et al. do not teach a method further comprising removing the complementary copy of the template sequence and performing a second round of sequencing. The Examiner's reliance on Soper et al. for teaching a sequencing method wherein after primer extension, the extension products are removed from the immobilized templates by denaturing and further, that following removal of the extension products, the biotinylated template is ready for "resequencing", if desired, is duly noted. The Office Action does, however, recognize that the combined teachings of Balasubramanian et al. and Soper et al. do not teach comparing the first and second rounds of sequencing to confirm sequencing data. The Parker et al. reference is relied upon for teaching a method wherein multiple sequences are obtained and then the sequences are aligned and compared with published sequences. Despite the Office Action's assertions pertaining to the alleged teachings of the cited references, the passages cited in these references and, moreover, the references viewed as a whole and taken in combination fail to teach or suggest the recited element of step (c) of claims

4, 35, and 36 because the references taken alone or in combination fail to teach or suggest regenerating immobilised single-stranded template molecules on an array.

Regenerating the immobilised single-stranded template molecules on the array or recovering the array, in turn, makes it possible in step (d) to perform a second round of sequencing of each of the immobilised single-stranded template nucleic acid molecules regenerated in step (c) by synthesising a second complementary copy of each of the template sequences, wherein said synthesizing involves repeated cycles of incorporating a single nucleotide into the second complementary copy and detecting incorporation of the single nucleotide into the second complementary copy on the array to generate a sequence of the second complementary copy (claims 4 and 35) or to perform a second round of sequencing of each of the immobilised single-stranded template nucleic acid molecules on the recovered array of sequenced immobilised single-stranded template nucleic acid molecules by simultaneously synthesising a second complementary copy of each of the template sequences, wherein said synthesizing involves repeated cycles of single nucleotide incorporation and detection of the single nucleotide incorporated, and incorporation and detection are performed on the array (claim 36). Regenerating each of the immobilised single-stranded template nucleic acid molecules or recovering an array of sequenced immobilised single-stranded template nucleic acid molecules and synthesizing and sequencing a second complementary copy of each of the immobilised single-stranded template nucleic acid molecules on the array renders it possible to positively ascribe a second complementary copy sequence read to a particular template nucleic acid molecule on the array.

As discussed herein above, the combined teachings of Balasubramanian et al., Cheeseman, Soper et al., and Parker et al. fail to teach or suggest step (c) of the claims as recited. Furthermore, step (c) provides the regenerated template that is acted upon in step (d), such that the combined references also fail to teach or suggest step (d).

For the sake of clarity, determining the sequences of the immobilised single-stranded template nucleic acid molecules by synthesising a first complementary copy of each of the template sequences, wherein said synthesising involves repeated cycles of incorporating a single

nucleotide into the first complementary copy and detecting incorporation of the single nucleotide into the first complementary copy on the array, thereby performing a first round of sequencing to generate a sequence of the first complementary copy as recited, for example, in step (b) of claim 4 confers the ability to positively ascribe a first complementary copy sequence read to a particular template nucleic acid molecule on the array.

The ability to ascribe a first and second complementary copy sequence read to a particular template nucleic acid molecule on the array enables comparison of the sequence of the first complementary copy detected in step (b) to the sequence of the second complementary copy detected in step (d) for each of the immobilized single-stranded template nucleic acid molecules. Definitive assignment of the first and second complementary copy sequence reads to a particular template nucleic acid molecule on the array thus makes it possible to confirm sequencing data of each of the immobilized single-stranded template nucleic acid molecules, as recited in step (e). As described above, the Office Action recognizes that the combined teachings of Balasubramanian et al. and Soper et al. do not teach comparing the first and second rounds of sequencing to confirm sequencing data, but relies on Parker et al. for teaching a method wherein multiple sequences are obtained, aligned, and compared with published sequences. However, an ordinarily skilled practitioner would appreciate that a gel-based sequencing method such as that described by Soper et al. or Parker et al. cannot be used for comparison of first and second sequencing reads for any individual template nucleic acid molecule in a pool of template nucleic acid molecules. Rather, the method necessarily provides an average of sequencing reads for several molecules albeit of the same or overlapping sequence.

Briefly, the method of Soper et al. is performed such that sequencing ladders are generated from any one of a plurality of labeled PCR products immobilized in a microreactor and there is no way to determine which sequencing ladder is an extension product of a particular immobilized labeled PCR product in any sequencing step, whether it is an initial sequencing step or an optional resequencing step. Thus, resequencing in the context of Soper et al. is only applicable to evaluating a population en masse, but is not capable of yielding any information that can be ascribed to a particular template molecule in the population. The Parker et al.

reference, like Soper et al., is directed to gel-based sequencing methods. The sequencing ladders of Parker et al. may be generated from any one of a plurality of double-stranded plasmid DNA molecules during the sequencing reaction and there is no way to determine which sequencing ladder is an extension product of any particular double-stranded plasmid DNA molecule. In light of the above, the optional resequencing of Soper et al. cannot be used to generate a first and second sequencing read ascribable to a particular template within the population of templates sequenced and thus cannot generate the necessary reagents for "comparing the sequence of the first complementary copy detected in step (b) to the sequence of the second complementary copy detected in step (d) for each of the immobilized single-stranded template nucleic acid molecules to confirm sequencing data of each of the immobilized single-stranded template nucleic acid molecules" as recited, for example, in step (e) of claim 4. Parker et al., moreover, fails to address this deficiency because it is also directed to gel-based sequencing methods and thus suffers at least from the same limitations.

Turning more particularly to the teachings of Parker et al. as they relate to "comparing the sequence of the first complementary copy detected in step (b) to the sequence of the second complementary copy detected in step (d) for each of the immobilized single-stranded template nucleic acid molecules to confirm sequencing data of each of the immobilized single-stranded template nucleic acid molecules" as recited, for example, in step (e) of claim 4, Applicant asserts that the method of Parker et al. fails to confirm sequencing data of a particular template within the population of templates sequenced, but rather compares sequencing data for populations of templates from different samples to known sequences in publicly available databases. In light of the above, the combined teachings of Balasubramanian et al., Cheeseman, Soper et al., and Parker et al. fail to teach or suggest step (e) of the instant claims.

Furthermore, when examined as a whole in accordance with MPEP 2141.02 (subsection VI), the Soper et al. and Parker et al. references and the gel-based sequencing method described therein are directed to a different purpose than that of the instant method. They are directed to sequencing and optionally resequencing nucleic acid templates (as in Soper et al.) to generate sequence information in a way that is focused on analyses of whole populations of nucleic acid

templates. As such, any comparison of such information is limited to comparisons of sequence information averaged across whole populations of different molecules, whether or not they have similar sequences. The methods described therein fail to yield information that can be used to compare a first and second read of a particular template molecule within a population of nucleic acid templates. This stands in contrast to the present invention, wherein a first and second round of sequencing can be performed on the same immobilized single-stranded template nucleic acid molecule, thereby making it possible to compare "the sequence of the first complementary copy detected in step (b) to the sequence of the second complementary copy detected in step (d) for each of the immobilized single-stranded template nucleic acid molecules to confirm sequencing data of each of the immobilized single-stranded template nucleic acid molecules" as recited in the instant claims. With this significant distinction in mind, Applicant asserts that the Soper et al. and Parker et al. references should be considered as whole entities in accordance with MPEP 2141.02 (subsection VI) and within this context, the propriety of selective excision of particular features of these references is diminished.

Moreover, in light of these significant distinctions, Applicant asserts that the method of the instant claims and the gel-based method of Soper et al. and Parker et al. should be viewed in light of suitability to their intended purposes. As detailed above, Applicant maintains that the intended purpose of the gel-based sequencing methods of Soper et al. and Parker et al. is to acquire sequence information relevant to a population en masse and an ordinarily skilled practitioner would appreciate that such methods are utterly defective with regard to generating sequencing information that can be ascribed to a particular template molecule within the population. In contrast, the present method possesses the distinctive functional capability to definitively ascribe a sequencing read to a particular template molecule in a population of templates and thus, one of its intended purposes is to compare first and second sequencing reads for particular templates within the larger population. Such considerations are in keeping with the tenets as set forth in MPEP 2144.07 and the Examiner is respectfully requested to accord appropriate weight to art recognized suitability for intended purposes in connection with these methods.

In light of the above, Applicant asserts that the combined teachings of Balasubramanian et al., Cheeseman, Soper et al., and Parker et al. fail to teach at least two recited elements of the claims and the alleged motivation to combine the teachings of these references to arrive at the claimed method is hampered by the fact that the suitability of the different sequencing methods to their intended purposes clearly reflects that they are not mutually interchangeable and this discrepancy is appreciated in the art.

In view of the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claims 4, 27-28, 30-31, 33, and 34-36 under 35 U.S.C. §103 and withdraw the rejection.

Claim 29 is rejected under § 103(a) as allegedly unpatentable over Balasubramanisn [*sic*] (i.e., Balasubramanian et al.; WO 01/57248; published 9/2001) as evidenced by Cheeseman (USPN 5,302,509; issued 1994) in view of Soper et al. (USPN 5,846,727) and Parker et al. (USPN 5,565,323) as applied to claims 4 and 27 above and further in view of Lackey et al. (USPN 5,652,126). In view of the clarifying amendments to the claims and arguments presented herein, this rejection is respectfully traversed.

The Office Action recognizes that the combined teachings of Balasubramanian et al. (as evidenced by Cheeseman), Soper et al., and Parker et al. do not teach a method wherein the double stranded anchor (which acts as a primer) comprises a recognition site for a restriction endonuclease. The Office Action relies on Lackey et al. for allegedly teaching a method that comprises synthesizing a complementary copy nucleic acid sequence using a template sequence. In a particular embodiment wherein a DNA primer/template with a single 3' ribonucleotide is used, the Office Action indicates that cleavage at the ribonucleotide residue, followed by separation and purification of the oligonucleotide product, results in a fully regenerated and reusable primer/template.

As indicated herein above, the combined teachings of Balasubramanian et al., Cheeseman, Soper et al., and Parker et al. fail to teach or suggest all of the recited elements of the instant claims. Arguments directed to this point are set forth above and are incorporated herein in their entirety in connection with the asserted rejection of claim 29. It is, moreover, noteworthy

that the deficiencies of Balasubramanian et al., Cheeseman, Soper et al., and Parker et al. are not remedied by the teachings of Lackey et al. The Office Action has, furthermore, failed to provide rationale to support the contention that it would allegedly have been obvious to one of ordinary skill in the art at the time of the invention to modify the alleged combination of the methods of Balasubramanian et al., Soper et al., and Parker et al. by using a double stranded anchor that acts as a primer and comprises a recognition site for a restriction endonuclease.

As stated by Applicant in previously presented arguments, Lackey et al. are silent with respect to sequencing the templates utilized therein to generate phosphorothioate oligonucleotides. The method of Lackey et al. is directed to cleaving phosphorothioate oligonucleotides to generate relatively cleavage resistant phosphorothioate oligonucleotides having properties that facilitate their separation and purification after synthesis. This reference has nothing to do with sequencing because the sequence of the template is already known. Furthermore, the methods of Lackey et al. are directed to the generation of pure populations of like oligonucleotides for use as probes. In contrast, the methods of Balasubramanian et al., Cheeseman, Soper et al., and Parker et al, are directed to methods of sequencing populations of many different nucleic acid templates and as such have intended purposes that bear no relationship to generating pure homogeneous populations of oligonucleotide probes. The Examiner is respectfully reminded that Lackey et al. should be read as a whole and accordingly, its intended purpose to generate pure homogeneous populations of oligonucleotide probes and principles of operation directed to same are significant in the context of this rejection. In light of the discrepancy in intended purposes of Balasubramanian et al., for example, and Lackey et al., Applicant asserts that the motivation to combine the teachings of these references is limited at best.

In view of the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of claim 29 under 35 U.S.C. §103 and withdraw the rejection.

Claim 32 is rejected under 35 USC § 103(a) as allegedly unpatentable over Balasubramanisn [*sic*] (i.e., Balasubramanian et al.; WO 01/57248; published 9/2001) as evidenced by Cheeseman (USPN 5,302,509; issued 1994) in view of Soper et al. (USPN

5,846,727) and Parker et al. (USPN 5,565,323) as applied to claims 4 and 31 above and further in view of Barnes (WO 01/57249; published 8/2001). In view of the clarifying amendments to the claims and arguments presented herein, this rejection is respectfully traversed.

The Office Action acknowledges that the combined teachings of Balasubramanian et al. (as evidenced by Cheeseman), Soper et al., and Parker et al. do not teach a method wherein the fluorescent nucleotides are detected using a microscope with total internal reflection based imaging. The Office Action relies on Barnes for teaching that using total internal reflection fluorescent microscopy makes it possible to achieve wide field imaging with single polymer sensitivity. Statements pertaining to the deficiencies of the combined teachings of Balasubramanian et al., Cheeseman, Soper et al., and Parker et al. are set forth in detail above and the aforementioned statements are incorporated herein by reference in their entireties. In short, at the very least, the combined teachings of Balasubramanian et al., Cheeseman, Soper et al., and Parker et al. fail to teach or suggest all of the recited elements of the instant claims. The teachings of Barnes fail to compensate for the aforementioned defects of these references in combination. That being the case, Applicant maintains that the teachings of Balasubramanian et al., Cheeseman et al., Soper et al., Parker et al., and Barnes would not lead an ordinarily skilled practitioner to arrive at the present invention.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw the rejection of claim 32 under 35 U.S.C. §103.

Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there

are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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Date: November 16, 2009

Enclosures: Petition for a One-Month Extension of Time
Request for Continued Examination